REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AND BOTULINUM TOXIN INJECTION AS NEUROREHABILITATION METHODS OF POST STROKE SPASTICITY

Thesis

Submitted for the partial fulfillment of M.Sc. Degree in Neuropsychiatry

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INTRODUCTION

Inspite of the improvement in the acute treatment of stroke, which means that mortality is reduced, the recovery of post-stroke has not changed much for decades Spasticity and its clinical implications are still poorly described ***(Mally et al, 2008).***

Surprisingly, there is no consensus concerning the number of patients developing spasticity or the relationship between spasticity and motor disabilities after stroke. Only few studies have addressed the prevalence of spasticity following stroke, its risk factors and its impact on quality of life with emphasis on disability in activities of daily living ***(Schinwelski & Sławek, 2010).***

A wide range of treatment options is available including; physical therapies, oral medications, intrathecal Baclofen, surgery, and botulinum toxin injections. For optimum results these treatments are usually used in combination in a multidisciplinary approach ***(Anwar K. and Barnes M.P., 2005)***.

Botulinum toxin through its chemodenervating effect is a potent muscle relaxing agent that is emerging as an effective therapy for treating patients with over-active muscles by pre-synaptic inhibition of acetylcholine release at the neuromuscular junction. Its action is confined to the cholinergic system ***(Rosales & Chua-Yap, 2008).***

Recently, Botulinum toxin type A (BTX-A) has been used for the control of focal spastic hypertonia in CNS injury and has been

successful in reducing upper extremity tone associated with spastic hypertonia as a result of stroke ***(Borg et al, 2011).***

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive way of producing potent changes in cortical excitability. Therefore, the application of rTMS was proposed to promote functional recovery in stroke patients, owing to the induced neuroplasticity ***(Kim, 2006)***.

AIM OF WORK

This study aims to detect whether the combination of Botulinum toxin injection and application of rTMS sessions on treating upper limb spasticity in stroke hemiplegic patients will be superior than using botulinum toxin alone or not.

Review of Literature

POST STROKE SPASTICITY

Background

It has been reported that up to 80% of stroke patients may have motor impairment immediately after stroke. One manifestation of this motor impairment is muscle spasticity, which can be defined as a velocity-dependent increase in resistance to passive stretch or movement. Upper motor neuron lesions caused by injury to the central nervous system (CNS) secondary to stroke, multiple sclerosis, cerebral palsy, head trauma or spinal cord trauma result in abnormal signaling between the CNS and the muscles, leading to increased muscle excitability ***(Barker and Mullooly, 1997)***.

Definition:

Spasticity is the manifestation of a lesion of the supraspinal motor pathways and is caused by adaptive changes in transmission in the spinal networks distal to a lesion of the descending motor pathways. Clinically, this implies increased muscle tone, enhanced tendon reflexes, involuntary reflex zones and clonus. In many cases, it does not permit patients to perform functionally significant voluntary movements or even occupy certain postures ***(Mayer, 1997)***.

Spasticity is only one of several components of the upper motor neuron (UMN) syndrome, known collectively as the 'positive' phenomena. Other components include tendon hyper-reflexia,

clonus, the clasp-knife phenomenon, flexor and extensor spasms, a Babinski sign, and spastic dystonia. Spasticity is a form of hypertonia due to hyperexcitable tonic stretch reflexes. It is distinguished from rigidity by its dependence upon the speed of the muscle stretch and by the presence of other positive UMN signs. Hyperactive spinal reflexes mediate most of these positive phenomena, while others are due to disordered control of voluntary movement or abnormal efferent drive. An UMN lesion disturbs the balance of supraspinal inhibitory and excitatory inputs, producing a state of net disinhibition of the spinal reflexes, including proprioceptive (stretch) and nociceptive (flexor withdrawal and extensor) reflexes. The clinical syndrome resulting from an UMN lesion depends more upon its location and extent, and the time since it has occurred, than on the pathology of the lesion. The change in spinal reflex excitability cannot simply be due to an imbalance in supraspinal control. The delayed onset after the lesion and the frequent reduction in reflex excitability over time, suggests plasticity in the central nervous system ***(Wilson et al., 1999).***

Physiology of normal muscle tone:

A motor unit consists of a motor neuron in the anterior gray column (horn) of the spinal cord and all the muscle fibers it supplies. In a large buttock muscle, such as the gluteus maximus, where fine control is unnecessary, a given motor neuron may supply as many as 200 muscle fibers. In contrast, in the small muscles of the hand or the intrinsic muscles of the eyeball, where fine control is required,

one nerve fiber supplies only a few muscle fibers. Every skeletal muscle, while resting, is in a partial state of contraction. This condition is referred to as muscle tone ***(Mayer, 1997).***

The stretch reflex arc is the most basic neural circuit contributing to normal muscle tone. It consists of contractile muscle fibers and sensory and motor neurons ***(Fig. 1).*** The cell body of the sensory neuron — the afferent limb of the arc- is located in the dorsal root ganglion of the spinal cord. The afferent limb of the sensory neuron originates from a specialized receptor organ (the muscle spindle) in the muscle. The muscle spindle is sensitive to physical deformation; stretching the muscle evokes an impulse in the muscle spindle, which is transmitted via the sensory neuron to the grey matter of the spinal cord. Here, the sensory neuron synapses with the motor neuron — the efferent limb of the arc. The cell body of the motor neuron lies within the anterior horn of the spinal cord, and the efferent limb exits via the anterior spinal root to innervate the contractile muscle fibers. The transmitted impulse results in muscle contraction. While agonist muscles contract in response to stretching, antagonist muscles must relax. Their relaxation is brought about via an inhibitory neuron within the spinal cord ***(Satkunam, 2003).***

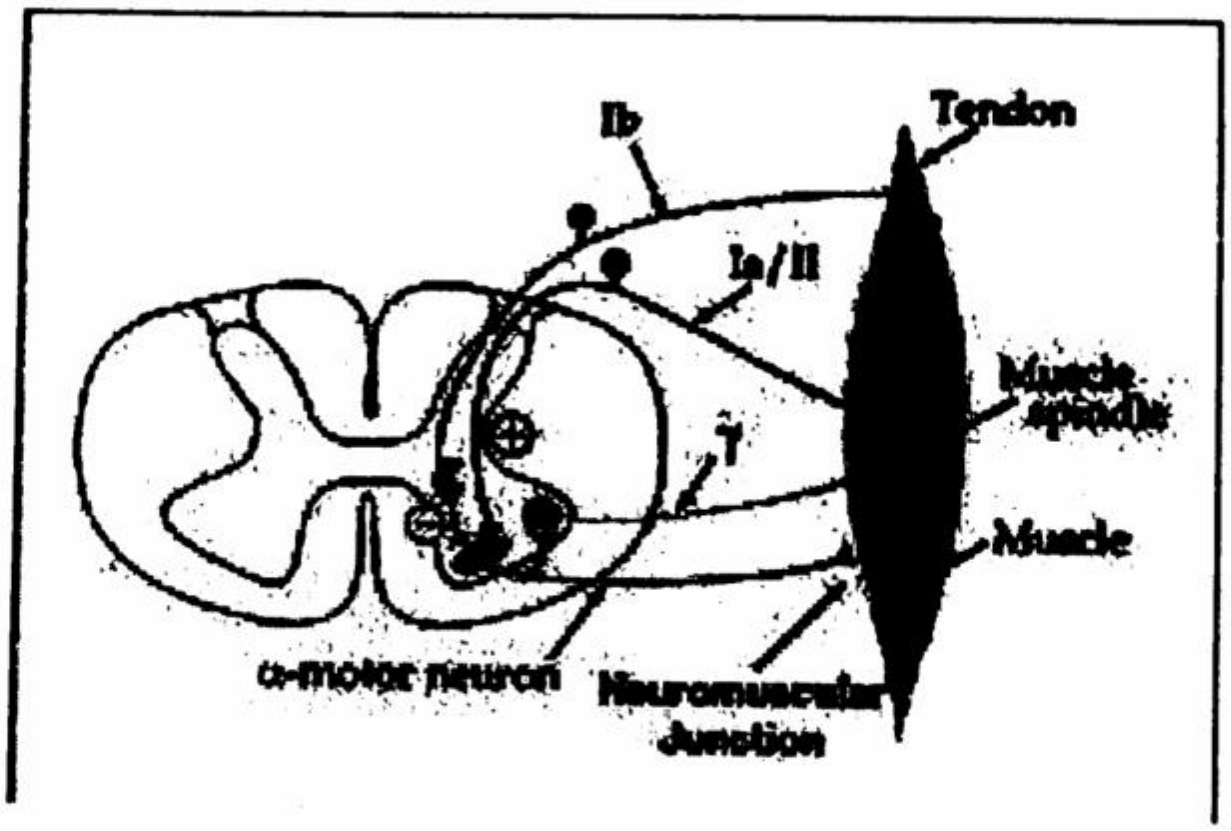

Figure 1: The stretch reflex arc *(Dressler, 2005).*

Pathophysology of spasticity:

The pathophysiologic basis of spasticity is incompletely understood. ***Nielson et al. (2007)*** have reviewed changes in cellular properties and transmission in a number of spinal reflex pathways, which may explain the increased stretch reflex excitability:

- Alterations in the balance of inputs from reticulospinal and other descending pathways to the motor and interneuronal circuits of the spinal cord.
- Absence of an intact corticospinal system.
- Loss of descending tonic or phasic excitatory and inhibitory inputs to the spinal motor apparatus.

Alterations in the segmental balance of excitatory and inhibitory control, denervation supersensitivity, and neuronal sprouting may be observed ***(Fig. 2)***.

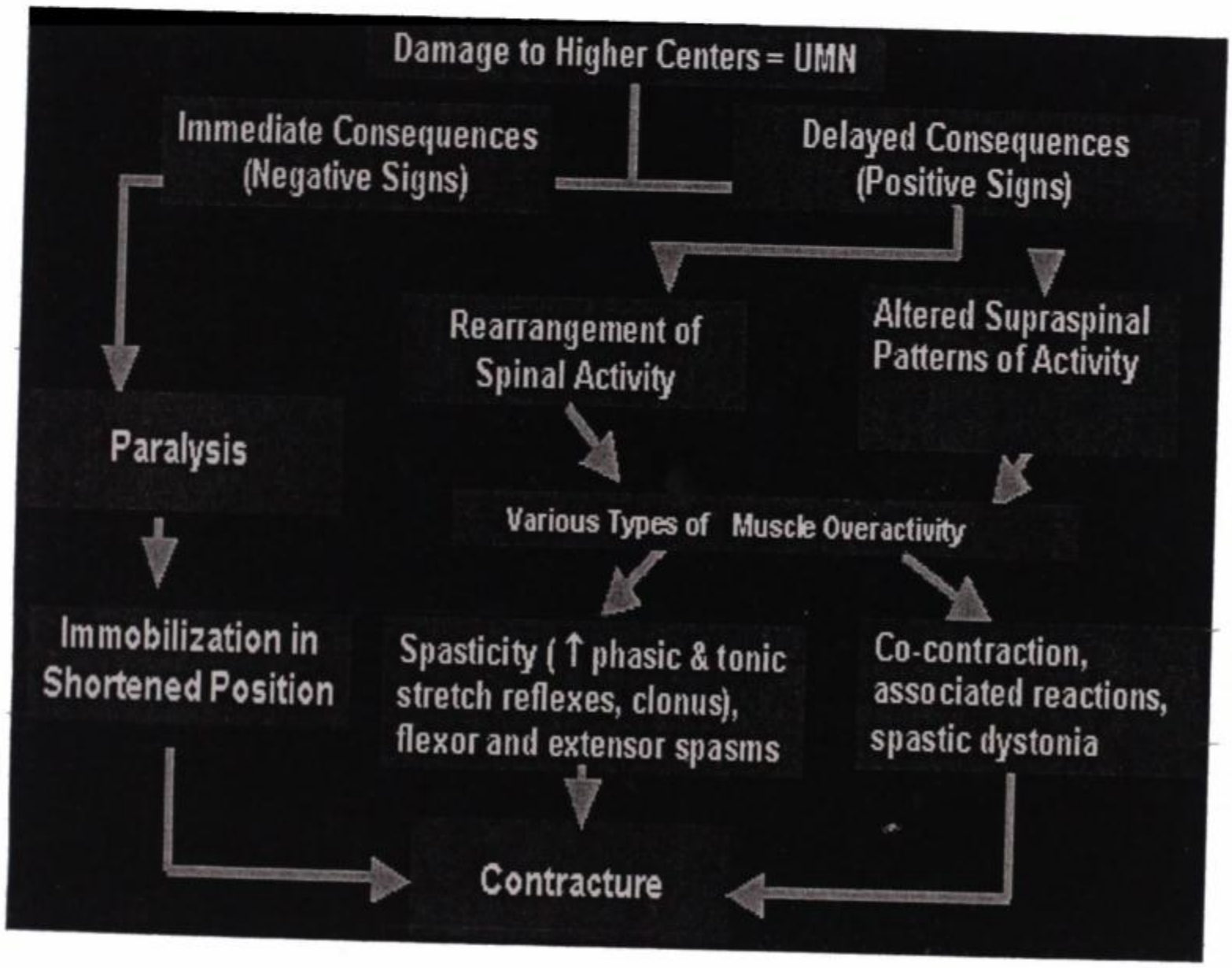

Figure 2: Sequences following Higher centre damage***(Dressler, 2005).***

The most basic neural circuit contributing to spastic hypertonia is the segmental reflex arc, which consists of muscle receptors, their central connections with spinal cord neurons, and the motoneuronal output to muscle. Within this arc, the alpha motor neuron (α MN) may be influenced by numerous excitatory and inhibitory modulatory synaptic influences, including:

(1) Excitatory post synaptic potentials from group **Ia** and **II** muscle spindle afferents.

(2) Inhibitory postsynaptic potentials from interneuronal connections from antagonistic muscles.

The inhibitory interneuron which produces inhibition of the activity in the antagonistic muscle is facilitated by descending tracts mainly corticospinal tracts.

(3) Presynaptic inhibition initiated by descending input.

Presynaptic inhibition is exerted by axons that end on primary afferent nerve terminals **(Ia)**, and that reduce the ability of sensory afferents to depolarize the postsynaptic membrane.

(4) Recurrent Renshaw cell mediated inhibition. This recurrent inhibition is an inhibitory feedback of α MN cell body by the inhibitory interneuron ***(Katz & Rymer, 1989).***

The alpha motor neuron and the muscle comprise the final common pathway in the expression of motor functions, including spasticity. There are numerous excitatory and inhibitory modulatory synaptic influences on this pathway. An imbalance in these influences results in hyperexcitability of the stretch reflex arc, which is thought to be the basis for spasticity. Some of the factors that play a role in suppressing hyperactivity of the final common pathway ***(Fig. 3)*** include cerebral inhibitory pathways (from the brain) and spinal mechanisms such as nonreciprocal **Ib** inhibition (from golgi

tendon organ receptors in tendons), presynaptic inhibition of the **Ia** terminal (at the axoaxonic synapse between 2 axons), reciprocal **Ia** inhibition (inhibition of antagonistic muscles) and recurrent Renshaw inhibition (inhibitory feedback of the alpha motor neuron cell body by the inhibitory interneuron) ***(Enoka, 2008)***.

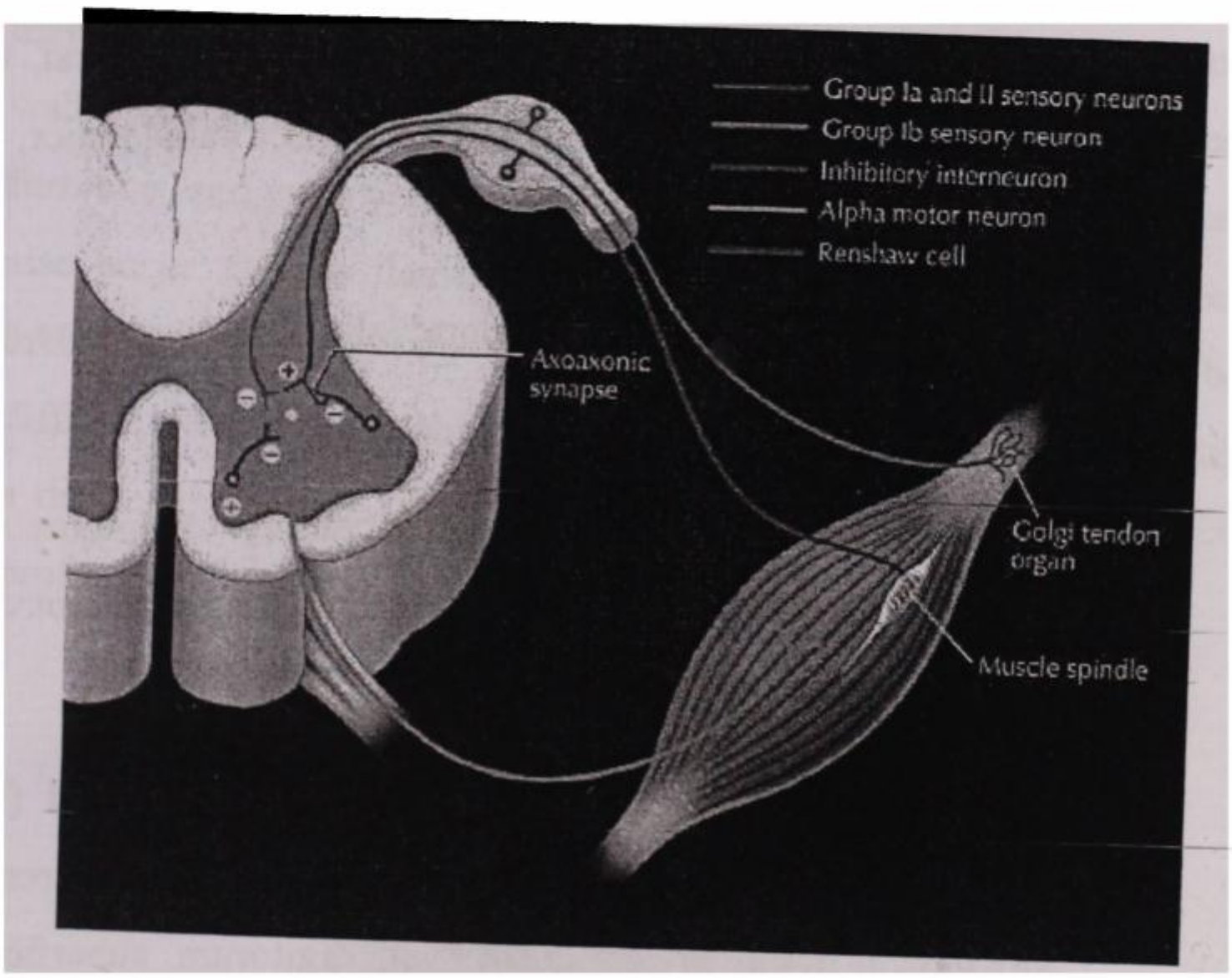

Figure 3: Potential spinal mechanisms of suppression of hyperactivity in the final common pathway (alpha motor neuron and muscle) ***(Satkunam, 2003).***

Once spasticity is established, the chronically shortened muscle may develop physical changes such as shortening and contracture that further contribute to muscle stiffness.

The pathophysiology varies depending on the site of the lesion but commonly develops in the antigravity muscles. For instance,

excessive muscle tone in the upper-extremity flexor muscles is prominent in spasticity following stroke ***(Pandyan et al., 2005)***.

Spasticity of the upper extremities

Muscles that often contribute to spastic adduction/internal rotation dysfunction of the shoulder include latissimus dorsi, teres major, the clavicular and sternal heads of pectoralis major, and subscapularis.

- In the flexed elbow, the brachioradialis is spastic more often than the biceps and brachialis.

- In the spastic flexed wrist, carpal tunnel symptoms may develop. Flexion with radial deviation implicates flexor carpi radialis overactivity.

- In the clenched fist, if the proximal interphalangeal (PIP) joints flex while the distal interphalangeal (DIP) joints remain extended, spasticity of the flexor digitorum superficialis (FDS) rather than the flexor digitorum profundus (FDP) may be suspected. A combined metacarpophalangeal flexion and PIP extension also may occur. A patient may be spastic in only one or two muscle slips of either FDP or FDS. Neurolysis with botulinum toxin is beneficial for spasticity of the intrinsic hand muscles because of their size and accessibility.

Flexed elbow

The patient typically presents with persistent elbow flexion during sitting ***(Fig.4),*** standing, and especially walking. Prolonged elbow flexion posturing is frequently associated with contracture. Stiffness is a frequently reported sensation. Patients complain that their elbow "rides up" (flexes markedly when they stand up and walk) and that their flexed elbow commonly hooks door frames, furniture, and even people. Shaking secondary to elbow clonus may also occur. Severe flexion posturing can lead to skin maceration, breakdown, and malodor in the antecubital fossa. Dressing can be difficult. Reaching for objects and bringing them to the body, closing a drawer or a door, and walking with a walker or crutch may be profoundly restricted.

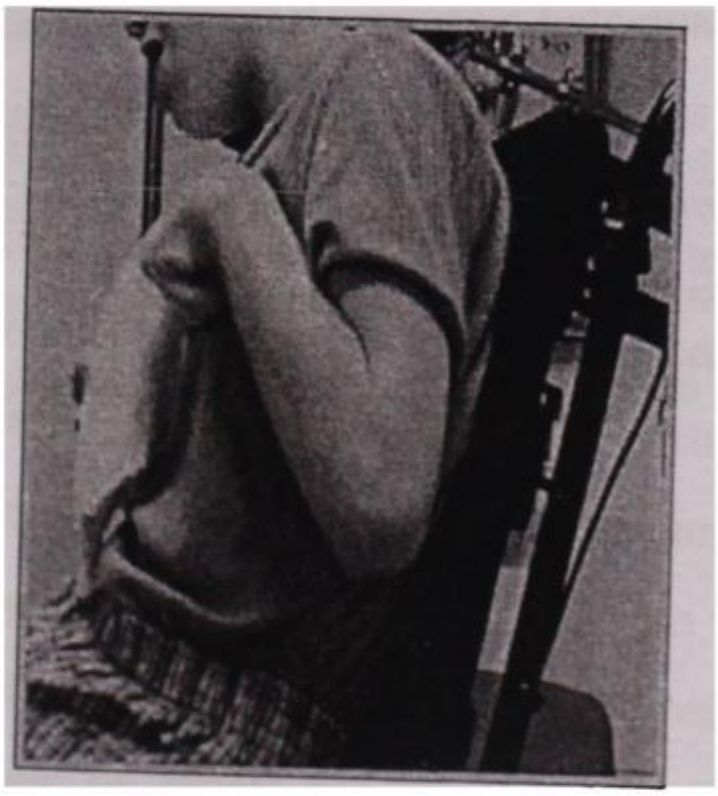

Figure 4 : Flexed elbow. The muscles contributing to flexed elbow are amenable to chemodenervation, neurolysis, and orthopedic lengthening ***(Mayer & Brashear, 2005).***

Flexed wrist

Muscles that potentially contribute to the flexed wrist deformity include the flexor carpi radialis, flexor carpi ulnaris, palmaris longus, flexor digitorum sublimis, flexor digitorum profundus, and, in cases where there is ulnar deviation, the extensor carpi ulnaris.

The patient typically presents with a wrist that is flexed, sometimes with radial deviation, sometimes with ulnar deviation. In many cases, a flexed wrist is associated with clenched fist deformity ***(Fig.5)***. The extrinsic finger flexors cross the wrist anterior to its axis of rotation and therefore act as accessory wrist flexors themselves. Passive stretching of stiff flexors can be uncomfortable or painful. Associated compression of the median nerve can produce carpal tunnel syndrome with hand pain. Severe flexion of the wrist hinders passive exercises, dressing, and washing. Wrist flexion posturing restricts hand placement during reaching, impairs positioning of objects held by the hand, and weakens grip strength.

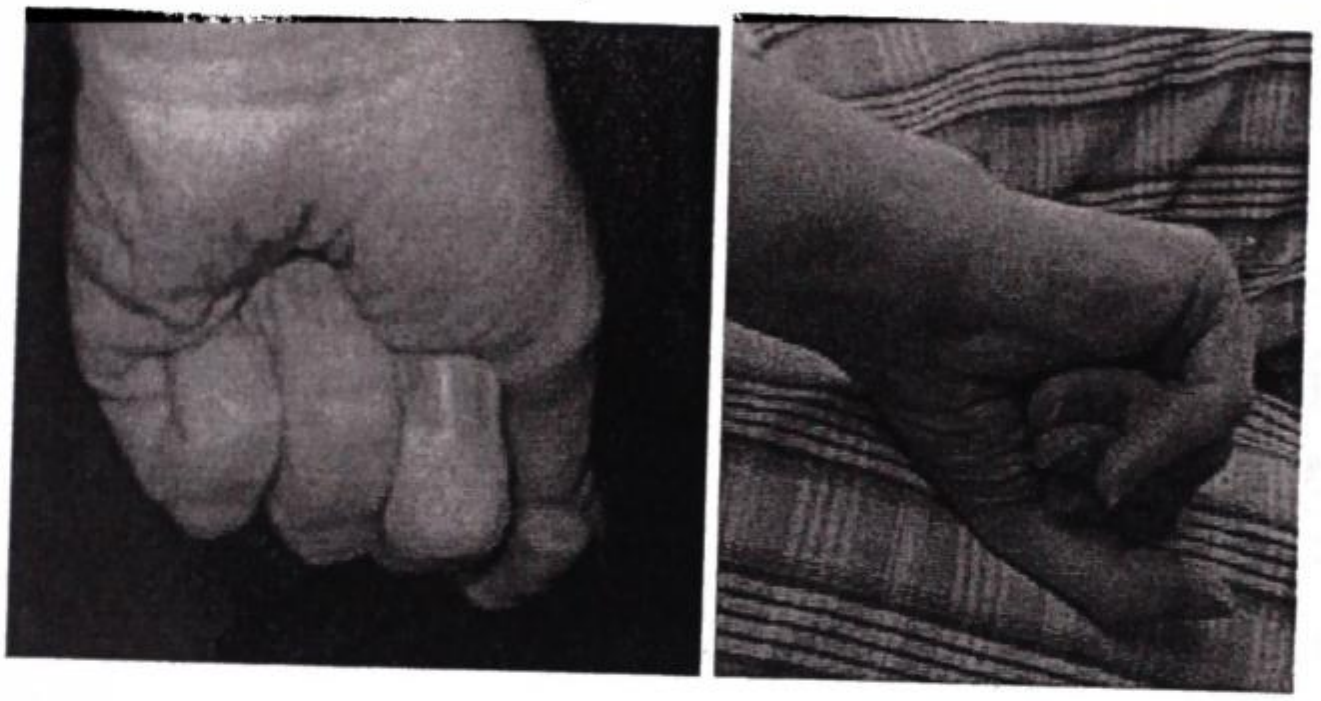

Figure 5: Clenched fist associated with ***(Mayer & Brashear, 2005).***

(a) Overactive flexor digitorum profundus is linked to flexion of the distal interphalangeal (DIP) joint.

(b) overactive flexor digitorum superficialis is linked to proximal interphalangeal joint flexion and DIP extension ***(Mayer)***

Assessment of spasticity

Spasticity creates great difficulty for both the patient and the clinician. Evaluation and interpretation of the tone disorders are complex, controversial, and subject to many misconceptions ***(Shiavi et al., 1997)***. It was mentioned that when spasticity is measured objectively, it is better to relate spasticity to function ***(Burridge et al, 2005)***. An important element of demonstrating the value of a certain treatment intervention is to measure its effectiveness. Evaluation may be done either by direct measurement of impairment or by indirect measurement of functional ability ***(Harris, 2000).***

Moreover, spasticity measurement should be correlated with other parameters including; clinical, biomechanical and neurophysiological parameters ***(Voerman et al., 2005)***.

A-Direct measurement of spasticity

Observation:

The patient should be placed in a comfortable supine lying position and observe any abnormal pattern that suggests the process of tone abnormalities. Also, any involuntary movement may be indicative of dystonia and complete absence of spontaneous activity of the subject may be indicative of hypotonia ***(O'sullivan and Schmitz, 1994).***

Passive movement:

The manual passive stretch maneuver consists of lengthening and shortening the muscle corresponding to a specific joint. Spasticity is detected by noting the degree of resistance offered by the muscles during passive movement ***(Dimitrijevic et al., 1991).*** There is a three-categories scale (mild, moderate and severe spasticity) which is widely used by physiotherapists, but it is unreliable with large inter-rater errors. The information gained through this rating scale might only be qualitative ***(Hass and Crow, 1995).***

Ashworth (1964) offered a gross clinical scale assessing muscle tone on a scale of zero (normal) to four (severe) but may lack

temporal and inter-examiner reproducibility. This scale suffers from clustering effect with most patients grouped in the middle grades. The patient is examined in a comfortable position, usually supine, and muscle tone is assessed bilaterally and separately for the upper and lower extremities. A modification of this scale had been created which added an additional intermediate grade (1+) and had been shown to have high inter-rater reliability when testing elbow flexors. It was mentioned that the clinical scales as Ashworth's and modified Ashworth's scales have high inter-rater reliability ***(Platz et al., 2005)***.

Modified Ashwoth Scale (MAS) ***(Pandyan et al, 1999)***

0 = No increase in muscle tone

1 = Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension

1+ = Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM

2 = More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved

3 = Considerable increase in muscle tone, passive movement difficult.

4 = Affected part(s) rigid in flexion or extension

Tendon jerk:

Eliciting the reflex in a number of tendons is a common clinical and bed side test which is generally easy to administer. But it provides a clinical impression which is highly subjective and it would be essential to supply a reproducible stimulus and measure the degree of deflection ***(Burry, 1992)***. Moreover, it was found that the use of tendon jerks in their simplest form is not reliable and any attempts of standardizing the test, makes the method too complex for the clinical setting ***(Bohannon and Andrews, 1990).***

Tardieu scale ***(Paulis et al, 2010)***

0= No resistance throughout the course of the passive movement.

1= Slight resistance throughout the course of passive movement, no clear catch at a precise angle.

2= Clear catch at a precise angle, interrupting the passive movement, followed by release.

3= Fatigable clonus with less than 10 seconds when maintaining the pressure and appearing at the precise angle

4 = Unfatigable clonus with more than 10 seconds when maintaining the pressure and appearing at a precise angle

5= Joint is immovable

B- Indirect measurement of spasticity:

Spasticity affects dexterity and functional activities. Therefore it may cause changes in the functional abilities of the patient. These changes may indicate change in the grade of spasticity. There are many available valid and reliable measurement of functional ability, but there are conflicting opinions about their validity in measuring spasticity. The functional measurements provide useful parameters of activities of daily living, but does not reflect spasticity perse ***(Pederson et al., 1997).***

Fugl-Meyer Scale:

This scale is an accurate and objective method of assessing function (but not necessarily spastichypertonia) in hemiplegic patient. It is based on the natural progression of functional return observed by previous investigators. This scale has intra-tester and inter-tester reliability, and can be completed in a period of 10 to 20 minutes ***(Fugl Meyer et al, 1985).***

Associated reactions:

Associated reactions in hemiplegia are defined as abnormal reflexive movement of the affected side, which would duplicate the typical stereotyped reaction that appear closely related to activity and effort on the non affected side of the patient. Both are seen difficult to quantify. This would be essential if associated reaction were used in measurement of spasiticity, as in a study compared with

isokinetic measurements. They use the goniometry to measure differences in joint position before and after a specified movement. The use of associated reaction in the measurement of spasticity appears to be of limited value ***(Dvir and Panturin, 1993).***

Oswestry Scale:

This scale can be defined as an ordinal scale that rates the stages and distribution of tone and quality of isolated active movement. Function is addressed by a generalized grade of either useful or non-useful movements. Also this scale attempts to consider the influence of posture and descending brain stem and spinal reflexes ***(Goff, 1976).***

Pendulum Test:

The pendulum test has been a frequently used to assess spasticity of the knee extensor muscle. In this test, the patient is instructed to lie in a supine lying position on a tilting table with both knees flexed over the edge of the table hanging both legs freely outside. He brings the leg to a horizontal position and then the limb is allowed to fall freely as the angle of the knee is recorded by an electrogoniometer which is fitted previously to the outer surface of the knee joint ***(Bajed and Bowman, 1982).***

Biomechanical investigation of spastic hypertonia:

The biomechanical investigations attempted to quantify changes in phasic and tonic reflex activity within the limb of spastic patients.

Quantitative observation can be made of torque (the amount of force elicited by moving a limb over a specified angle), threshold (particular angle where torque or electromyography (EMG) records significant increase) and EMG (rectified signal analysis from superficial muscle groups) ***(Katz and Rymer, 1989).***

Electrophysiological testing:

There were a wide variety of electrophysiologic reflex studies that had been performed to assess spasticity and explore neuronal circuits within the spinal cord. The M-response is a compound muscle action potential generated by maximally stimulating a peripheral nerve and recording over a muscle innervated by that nerve. The H-reflex is not a direct response of muscle to stimulation of its motor nerve, but rather a reflex similar to muscle stretch reflex. It was stated that the most common methods to measure spasticity objectively is H reflex. This method is characterized by moderate reliability and sensitivity ***(Eisen and Odusote, 1999; Voerman et al. 2005).***

The H-reflex studies may be influenced by changes in stimulation frequency, patient relaxation, limb position or changes in head and neck position ***(Hugon, 1993).*** In addition, the H/M ratio has been used to assess the excitability of the motor nucleus by determining the percentage of motor neurons activated via the H-reflex in comparison to direct activation of the motor neurones. There is increase in H/M ratio in the spastic phase of hemiplegia and spinal cord injuries ***(Little and Halar, 1985).***

BOTULINUM TOXIN IN SPASTICITY

Introduction

Botulinum toxin type A (BTX-A) is one of the most potent and lethal biologic neurotoxin. It has been proven successful in the treatment of various neurologic and ophthalmologic disorders and is now routinely used in adult focal dystonia ***(Jankovic and Brin, 1991).***

Trials have reported that treating upper limb spasticity due to stroke with botulinum toxin results in a measurable reduction in resistance to passive movement (muscle tone), which is evident by 1–2 weeks post-treatment. The treatment effect usually lasts for 3–4 months. Although trials vary in the dose and type of botulinum toxin used, the magnitude of initial change in muscle tone/spasticity was approximately a one-point decrease on the Modified Ashworth Scale (MAS), which reflects a clinically significant improvement ***(Elia et al,2009).***

HISTORY

Justinus Kerner first recognized the potential for a therapeutic use for BTX in 1817. He recognized that toxin paralyzed muscles and parasympathetic function and proposed that it could be used as a therapeutic agent ***(Erbguth and Naumannn,1999)***

Van Ermengem, in 1895, discovered Clostridium botulinum, a gram-negative anaerobic bacterium, and its potent neurotoxin during an outbreak of food poisoning in Ellezelles, Belgium. BTX is recognized as a most potent poison and has been feared as a biological weapon. In 1981 the first report of the clinical use of intramuscular injections of BTX in the treatment of strabismus appeared ***(Devriese, 1999)***

Das and Park, in 1989, first reported the use of BTX in the treatment of spasticity in adults. Six patients improved when stroke-related spasticity was treated with botulinum toxin in an open study ***(Das and Park, 1989)***

In 1989 the Food and Drug administration (FDA) in the United States (US) approved botulinum toxin A (Botox, BTXA) as a therapeutic agent in patients with strabismus, blepharospasm, and other facial nerve disorders, including hemifacial spasm. In 2000, the FDA approved Botox and botulinum toxin type B (Myobloc, BTX B) as treatments for cervical dystonia. Regulatory agencies in some European countries have approved BTX A for the treatment of adult and childhood spasticity. Its widest application is still in the treatment of disorders manifested by abnormal, excessive, or inappropriate muscle contractions. However, its use is rapidly expanding to include treatment of a variety of ophthalmological, gastrointestinal, urological, orthopaedic, dermatological, secretory, painful, and cosmetic disorders ***(Eleopra et al, 2004).***

Clinical effects of rTMS

1 Hz stimulation

Initial studies with 1 Hz rTMS concentrated on examining the immediate effects after a single treatment session. ***Mansur et al (2005)***, ***Takeuchi et al (2008)*** and ***Nowak et al (2008)*** all reported a short-term improvement in motor performance of hand functions by approximately 10–20%. There have also been a small number of investigations of the longer term effects of repeated 1 Hz rTMS ***(Kirton et al, 2008)***

Mally and Dinya (2008) found a significant improvement in movement induction and behavior after 1 Hz rTMS over the unaffected hemisphere. Intriguingly, rTMS was frequently applied over the affected hemisphere rather than the unaffected hemisphere.

A study confirming these results, however, used either 1 Hz over the unaffected hemisphere or 3 Hz over the affected hemisphere patients within 2 weeks of stroke can enhance recovery. The outcome was more pronounced in 1 Hz group at 3 months ***(Khedr et al, 2009).***

3 Hz stimulation

As with 1 Hz stimulation, most of the studies with excitatory forms of rTMS have used a single session approach ***(Kim et al 2006; Yozbatiran et al 2009; Talelli & Rothwell, 2006)*** of different high-frequency stimulations (10 Hz, 20 Hz, as well as theta burst stimulations) respectively.

One study of long term treatment with excitatory rTMS was that of in which he found that 10 consecutive days of rTMS applied at 3 Hz with intensity 120% RMT on the affected motor area improved durably the clinical outcome in early stroke patients ***(Khedr et al, 2009)***.

It was found that a single session of low-frequency rTMS over the unaffected hemisphere up-regulated the corticospinal excitability of the affected hemisphere as well as does the high-frequency rTMS over the affected hemisphere. These data are compatible with the theory of interhemispheric balance in which reducing the excitability of the non-stroke hemisphere removes tonic inhibition of the stroke hemisphere and hence increases its excitability. However, applying 3 Hz over the affected hemisphere only increased cortical excitability of affected hemisphere without changes of unaffected hemisphere ***(Takeuchi et al 2008 & Kirton et al, 2008).***

Neuroimaging studies showed increased activity of intact hemisphere with movements of the paretic hand in patients with motor impairment ***(Calautti & Baron, 2003).*** The role of activity in the intact hemisphere on motor control, is still under investigation, it varies depending on:

- Lesion site
- Time from stroke
- Magnitude of impairment ***(Ward et al, 2004)***

Patients with stroke experience changes in motor cortical excitability and an abnormally high interhemispheric inhibition from intact hemisphere to lesioned hemisphere ***(Fig. 7)*** with movements of the paretic hand that is more prominent in cases with more substantial motor impairment ***(Murase et al, 2004)***.

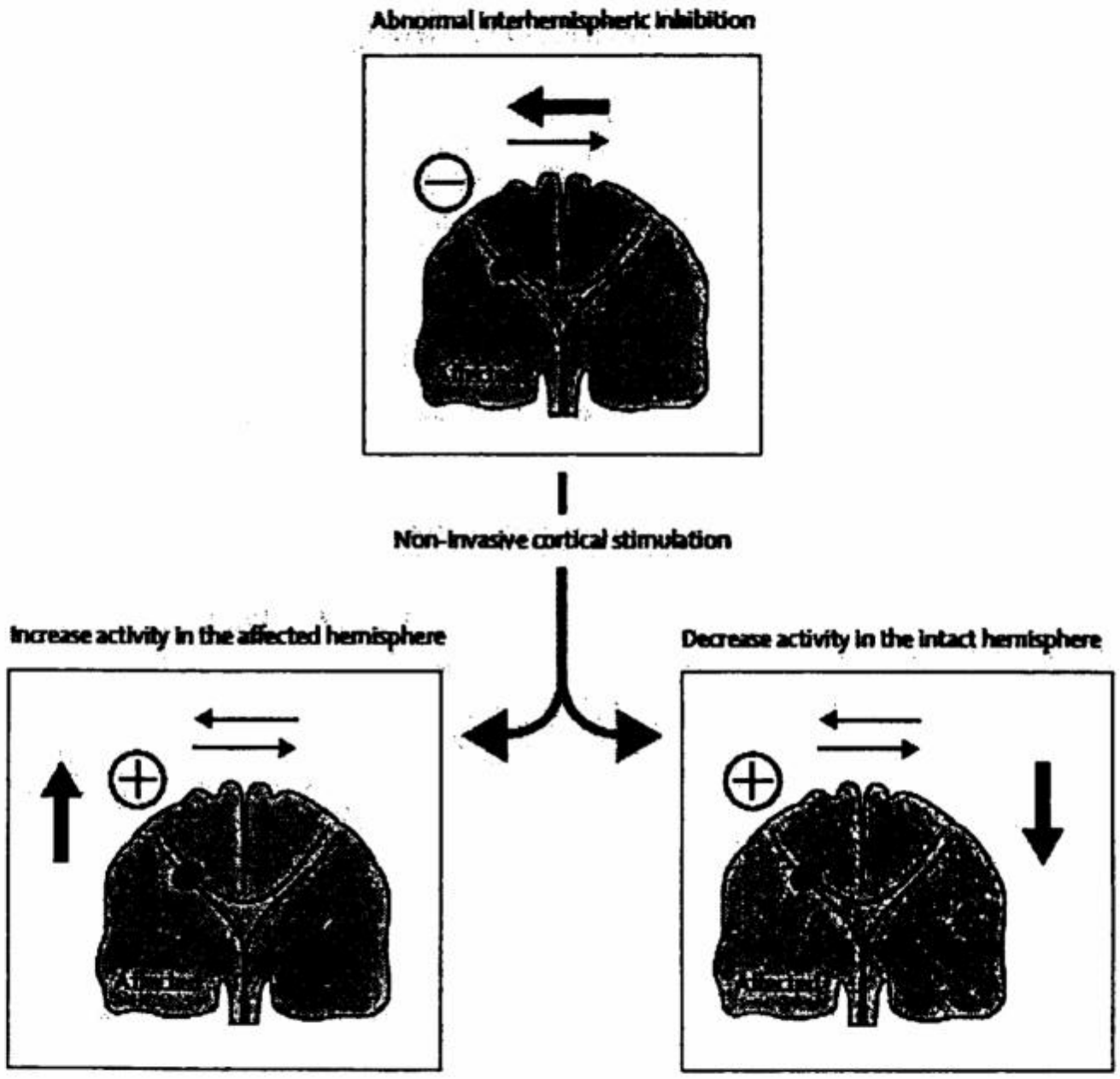

Figure7: Targets for intervention strategies based on possible pathophysiological mechanisms upregulation of excitability of the motor cortex of the affected hemisphere and downregulation of excitability of the motor cortex in the intact hemisphere ***(Hummel & Cohen, 2006).***

Safety of rTMS:

Strict rules of use and training protocols have made rTMS generally safe ***(D'Agati et al, 2010)***, with rare side effects ***(Table 3)***

Table 3: Potential side effects of rTMS

	Low frequency rTMS	**High frequency rTMS**
Seizure induction	Rare (usually protective effect)	Possible (1.4% crude risk estimate in epileptic patients; less than 1% in normals)
Transient acute hypomania induction	Rare	Possible following left prefrontal stimulation
Syncope	Possible as epiphenomenon (i.e., not related to direct brain effect)	
Transient headache, local pain, neck pain, toothache, paresthesia	Frequent	Frequent
Transient hearing changes	Possible	Possible
Transient cognitive/neuropsychologial changes	Overall negligible	Overall negligible
Burns from scalp electrodes	Not reported	Occasionally reported
Induced currents in electrical circuits	Theoretically possible, but described malfunction only if TMS is delivered in close proximity with the electric device (pace-makers).	
Other biological transient effects	Not reported	Transient hormone (TSH),and blood lactate level changes

(Rossi et al, 2009)

MATERIALS AND METHODS

SUBJECTS AND METHODS

This prospective, randomized comparative study was approved by Medical Research Ethical Committee. The study was held in the period from March to September 2011.

Twenty patients (10 males, 10 females) who aged between 29 to 72 years suffering from hemiplegia due to cerebro-vascular stroke (based on clinical and radiological data) were recruited from the neurology outpatient clinic Kasr ElAini Hospital.

PATIENTS:

Inclusion criteria:

All included patients suffered from

1. A stroke not less than 3 months, and not more than 2 years previously at the time of study, and who did not respond to conventional anti-spasticity management.

2. Symptoms and signs that were sufficiently impairing their quality of life or interfering with activities of daily living (ADL).

3. A moderate degree of spasticity in at least one group of muscles according to the Modified Ashowrth Scale (MAS: 1+ to 3), with preserved voluntary movements in at least one group of muscles.

Exclusion criteria:

1. History of recurrent strokes.
2. Psychiatric disorders, impaired perception and/or cognition and non-cooperative patients.
3. Seizures.
4. Any intracranial metallic implant.
5. Patients with fixed contractures and deformities.
6. Previous exposure to BTX-A, any neuromuscular disease, or treatment with drugs affecting the neuromuscular junction.
7. Severe renal or hepatic impairment and any other severe metabolic derangements.

METHODS:

The following was done for all patients:

A written, informed consent was obtained prior to the study following an explanation of the nature, duration, and purpose of the study

- Routine neurological- clinical- examination was performed to evaluate the present motor dysfunction.
- The spasticity was evaluated according to (MAS) and Tardieu scale.
- The muscle power was evaluated using Medical Research Council (MRC) scale.

Modified Ashwoth Scale (MAS)

0 = No increase in muscle tone

1 = Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension

1+ = Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM

2 = More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved

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4 = Affected part(s) rigid in flexion or extension

Tardieu scale

0= No resistance throughout the course of the passive movement.

1= Slight resistance throughout the course of passive movement, no clear catch at a precise angle.

2= Clear catch at a precise angle, interrupting the passive movement, followed by release.

3= Fatigable clonus with less than 10 seconds when maintaining the pressure and appearing at the precise angle

4 = Unfatigable clonus with more than 10 seconds when maintaining the pressure and appearing at a precise angle

5= Joint is immovable

Medical Research Council (MRC) scale

0= No movement

1= Palpable contraction, no visible movement

2= Movement but only with gravity eliminated

3= Movement against gravity

4= Movement against resistance but weaker than normal

5= Normal power

N.B.

- Range of motion (ROM) will be evaluated using Goniometer.
- Patients will be allocated randomly to one of the two treatment groups. Ten patients in each:
  - ✓The first group (A) will be subjected to Botulinum toxin injection only.
  - ✓The second group (B) will be subjected to Botulinum toxin injection in addition to rTMS.

Botulinum toxin injection protocol

- The formulation and preparation of botulinum toxin type A (BOTOX®) were performed ***(Childers et al, 2004).***
- Both groups (A and B) were injected as follows:
    - The dose of botulinum toxin was administered according to each patient's individual pattern of spasticity, with doses not exceeding 400 U per session and not more than 50 U per single injection site. The dosage of BTX-A ranged 100–400 U.
    - The dilution was standardized: one vial (100 U) was diluted with 2 ml normal saline (5 U/0.1ml).
    - The injections were administered using anatomical landmarks and under EMG guidance with identification of target muscles by recording the muscle activity during active or passive movements.
- A chart for each patient was set for recording muscle power (MRC score), grade of spasticity, ROM and BTX-A doses of the injected muscles based on clinical observation and examination.

Repetitive Transcranial Magnetic Stimulation (rTMS) protocol

- Group (B) was followed by rTMS applied to non-lesioned cerebral hemisphere over the target motor cortex area corresponding to the paretic hand.
- A MagStim Rapid magnetic stimulator (Magstim Company, Whitland, Wales, UK), connected with a figure-of-eight coil with a diameter of 70 mm, was used to deliver rTMS over the scalp site corresponding to the upper limb area of primary motor cortex.
- Low-frequency rTMS was applied at subthreshold intensity.
- The figure-of-eight coil was applied tangentially to the subject's head surface, with the handle pointing posteriorly and positioned at 45° with respect to midsagittal axis of the head then moved forwards at 1-cm steps to find the optimal scalp position to elicit motor responses in the contralateral thumb ("motor hot spot").
- Once the hot spot was identified, the Resting Motor Threshold (RMT) was determined as the lowest stimulation intensity that produced a visible abduction of the thumb contralateral to the stimulated hemisphere.
- One train of 900 pulses at 1 Hz was applied and stimulation intensity was set to 90% RMT with a total duration of 15 minutes.

- Each patient will receive 10 sessions over 2 weeks (5 sessions per week)

General remarks:

- All patients in both groups will be subjected to intense traditional physiotherapy program after injection that will include splinting, inhibition modalities, prolonged stretching (Bobath approach) and strengthening exercise.
- They were also asked to maintain the same rehabilitation regimens throughout the study (the same number of hours spent daily on physiotherapy).
- Patients were allowed to continue with their current therapy, with dosages maintained at a stable level throughout the study.

Follow up:

- Follow up was done at 2, 6 and 12 weeks post-injection.
- At each follow-up visit, the overall response to treatment was evaluated with the use of MAS, TS and ROM.
- The scores were compared with the baseline status

Statistical methods:

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Mann Whitney *U* test for independent samples. Within group comparison of numerical variables was done using Wilcoxon signed rank test for paired (matched) samples. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Spearman rank correlation equation for non-normal variables. *p* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

RESULTS

RESULTS

The current prospective study included 20 patients (10 males, 10 females) who aged between 29 and 72 years suffering from hemiplegia due to cerebro-vascular stroke (based on clinical and radiological data)

- The patients were divided randomly into two groups (10 patients each)

Group (A): recieved Botulinum toxin injection only.

Group (B): received Botulinum toxin followed by rTMS applied to contralateral cerebral hemisphere

All patients received physiotherapy program three times a week that included stretching exercise for injected spastic muscles and strengthening techniques for antagonistic weak muscles

- All cases were assessed at baseline. Follow up was performed at 2, 6 and 12 weeks post injection.

- Assessments included Range of motion (ROM), the Modified Ashworth Scale (MAS) and Tardieu scale (TS) for both the elbow and wrist joints.

Demographic data:

Group A:

- Composed of 10 patients (5 females and 5 males).
- Their age ranged from 29 to 72 years old (mean± SD= 55.4±15.665) with stroke duration ranging from 9-18 months (Mean± SD=12.70± 3.093).
- Four patients with right sided weakness and 6 patients with left sided weakness
- The main risk factors within this group were : Hypertension (8 patients), Diabetes (7 patients) Dyslipidemia (5 patients), Smoking (4 patients) and valvular heart disease (2 patients).
- Patients received Botox ® injection (Range: 300-400 U, Mean± SD 360 ± 31.623)

Group B:

- Composed of 10 patients (5 females and 5 males).
- Their ages ranged from 49-70 years (Mean ± SD: 58.7 ± 6.667) with stroke duration ranged from 6-10 months (Mean ± SD:13.30 ± 7.558)
- Five patients with right sided weakness and 5 patients with left sided weakness.
- The main risk factors within this group were :Hypertension (9 patients), Diabetes (6 patients), Dyslipidemia (5 patients),

Smoking (5 patients) and valvular heart disease was seen in 2 patients.

- They received Botox injection 250-400 U (Mean ± SD:355.0 ± 43.780)
- In addition they were subjected to rTMS; 10 sessions over 2 weeks.

The demographic characteristics of the subjects did not differ significantly between the two groups ***(Table 4)***

Table 4: Demographic data of all included patients in both groups in the study.

	Group A (n=10)	Group B (n=10)
Age (yrs) Range Mean± SD	 29-72 55.4±15.665	 49-70 58.7 ± 6.667
P value	0.762	
Sex (female / male)	5/5	5/5
Stroke duration (months) Range Mean ±SD	 9-18 12.70± 3.093	 6-10 13.30 ± 7.558
P value	0.361	
Risk Factors		
Diabetes	7	6
Hypertension	8	9
Dyslipidemia	5	5
Smoking	4	5
Valvular heart disease	2	2

- **BASELINE DATA**

Group A

- Using goniometry; to measure range of motion (ROM), ROM for the elbow: 10-20°, Mean ±SD: 12.1± 5.101) and ROM for the wrist: 5-10 °Mean ±SD: 7 ± 2.123)
- The Modified Ashworth score was the same for both the elbow and wrist joints (range: 2–3)
- Tardieu scale at the elbow joint was 2- 3 while at the wrist was 3- 4

Group B

- The range of motion (ROM) for extension at the elbow was 10-20°, Mean ±SD: 11.00 ± 6.33) and that of wrist was 6-10 °, Mean ±SD: 8 ± 2.563)
- The Modified Ashworth score was the same for both the elbow and wrist joints (range: 2–3)
- Tardieu scale at the elbow joint was 2- 3 while at the wrist was 3- 4.

- **POST INJECTION**
  - **Range of motion**
    - ***At 2 weeks:***

- **Group A** showed extension at the elbow (Range:20-30°, Mean± SD 21.00±3.162) ***(Table 5; Fig.8)*** and extension at wrist showed (Range:10-30°, Mean± SD 16.50±8.18) ***(Table 6; Fig.9).*** While in **Group B,** elbow extension was (Range: 10-

30°, Mean± SD: 22.00±6.33) and extension at the wrist (Range: 0-15°, Mean± SD:9.50±4.378)

- **Group B** showed almost the same results as Group A.
- Both groups showed high statistical significance in comparison to baseline ($p \leq 0.005$).

- ***At 6 &12 weeks:***
  - **Group A** showed more extension at the elbow (Range:30-60°, Mean± SD 45.00±8.50)at week 6 and further improvement was noticed at **week** 12 (Range: 35-70, Mean± SD: 49.50± 9.85). At the wrist, marked and persistent (plateau) improvement (Range: 20-35°, Mean ±SD:27.50 ±5.40) was seen in comparison to baseline **($p \leq 0.005$).**
  - As for **Group B,** more or less similar results to group A were obtained at both the elbow and wrist joints with no significant difference between the 2 groups (p=0.144) ***(Table 5; Fig.9)***

Table 5: Summary (comparison) of Range of motion (ROM) at the Elbow between the 2 groups throughout the study.

Range of Motion (ROM) Elbow	Group A (n=10)	Group B (n=10)
BASELINE		
Range	10 – 20	10 - 20
Mean± SD	12.1 ± 5.101	11.00 ± 6.33
P value	0.690	
WEEK 2		
Range	20-30	10-30
Mean± SD	21.00 ± 3.162	22.00 ± 6.325
P value	0.582	
WEEK 6		
Range	30-60	30-60
Mean± SD	45.00 ± 8.498	50.00 ± 9.428
P value	0.172	
WEEK 12		
Range	35-70	40-70
Mean± SD	49.50 ± 9.846	55.50 ± 10.395
P value	0.145	

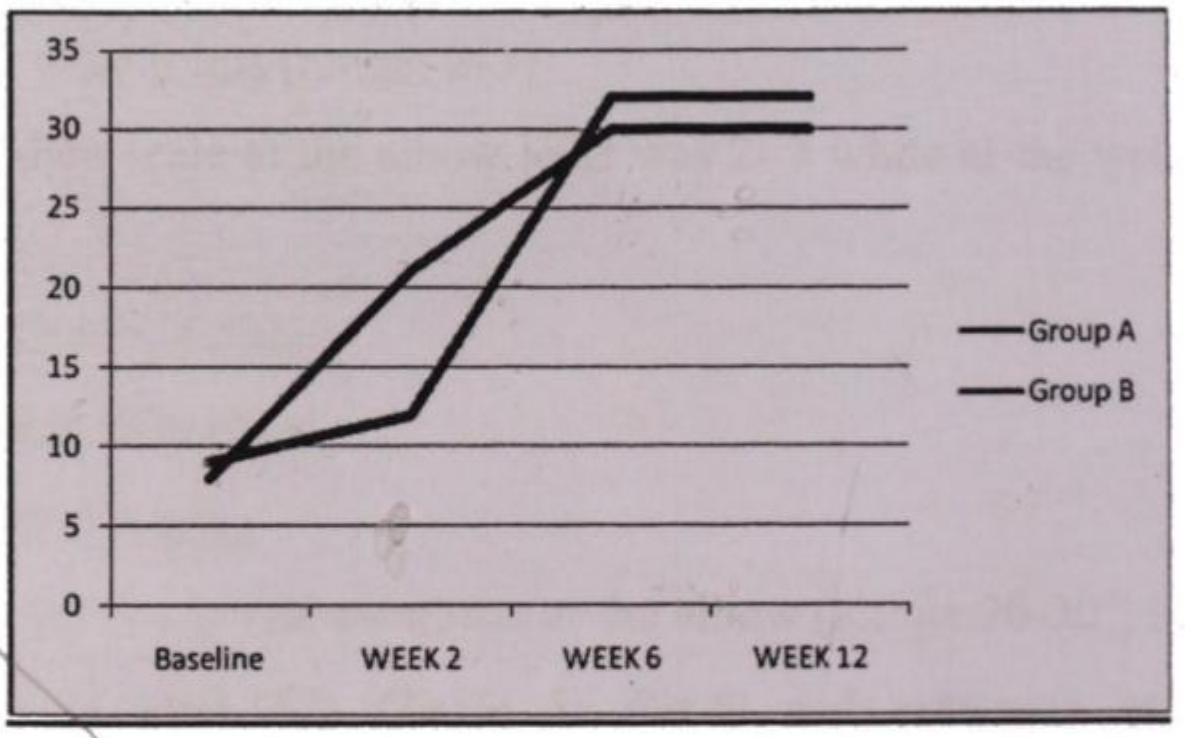

Figure 8: showing increase in the ROM at the elbow joint in both groups with more apparent improvement in group A (botox only).

Table 6 : Summary (comparison) of Range of motion (ROM) at the wrist in the 2 groups

Range of Motion (ROM) Wrist	Group A (n=10)	Group B (n=10)
BASELINE		
Range	5 - 10	6 – 10
Mean± SD	7 ± 2.123	8 ± 2.563
P value	0.395	
WEEK 2		
Range	10 - 30	0 – 15
Mean± SD	16.5 ± 8.182	9.50 ± 4.378
P value	0.046	
WEEK 6		
Range	20 - 35	20 - 35
Mean± SD	27.5 ± 5.401	28.0 ± 4.830
P value	0.897	
WEEK 12		
Range	20 - 35	20 - 35
Mean± SD	27.5 ± 5.401	27.5 ± 5.401
P value	0.897	

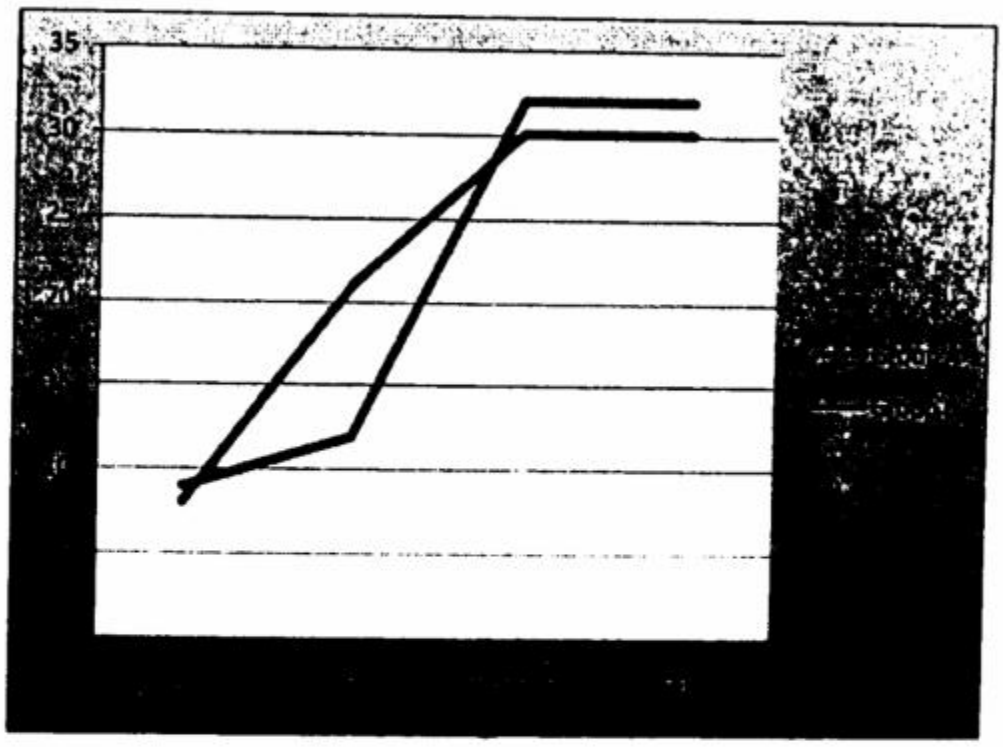

Figure 9: showing increase in the ROM at the wrist joint in both groups similar to that at the elbow joint

➢ **Modified Ashworth Scale (MAS)**

- At baseline, the Modified Ashworth score was the same for both the elbow and wrist joints (range: 2–3, p value= 0.72 and 0.639 respectively) in both groups.
- Clinical improvement was noticed at 2 weeks after BTX-A injections, as shown by a decrement of Ashworth scores (range 1^{+} - 2, P =0.002, ***Table 7***).
- The clinical benefit was more evident at 6 weeks (range: 1 – 1+ p=0.002).
- However, at week 12 worsening in MAS was seen at the elbow joint (range 2-3) in both groups of the study.
- 100% of subjects achieved at least a 1- point decrease on MAS scores in at least 1 joint.
- There were statistically significant improvements in scores at each point in comparison to baseline till week 6 in both groups with no significant difference between the 2 groups.
- Despite the decline documented in MAS in both groups at the end of the study (week 12), It has to be mentioned that for 70% of group A cases MAS was 3 at baseline while at week 12, MAS became 2 denoting that the positive effect of BTX-A was still present ***(Table 7).***

Table 7: *Summary of the MAS for both the elbow and wrist joints in both groups from baseline to the end of the study.*

Group A				
ELBOW				
Range	2 - 3 (30%) - (70%)	1+ 2 (30%) - (70%)	1 - 1+ (20%) - (80%)	2 - 3 (70%) - (30%)
P value		0.002*	0.002*	0.004*
WRIST				
Range	2 - 3 (50%) - (50%)	1+ - 2 (30%) - (70%)	1 - 1+ (20%) - (80%)	1 – 1+ (30%) - (70%)
p value		0.005*	0.004*	0.004*
Group B				
ELBOW				
Range	2 – 3 (50%) - (50%)	1+ - 2 (40 %) - (60%)	1 - 1+ (40 %) - (60%)	2 - 3 (60 %) - (40%)
P value		0.005*	0.004*	0.004*
WRIST				
Range	2 - 3 (70%) - (30%)	1+ 2 (70%) - (30%)	1 - 1+ (60%) - (40%)	1 - 1+ (60%) - (40%)
P value		0.003*	0.004*	0.003*

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Group	No	Age	Sex	Stroke duration	MRC			
					ELBOW		WRIST	
					Flexion	Extension	Flexion	Extension
B	1	63	male	9 ms	3	2	2	1
	2	53	female	6 ms	2	1	2	1
	3	70	female	8 ms	2	1	3	2
	4	49	male	7 ms	1	0	1	0
	5	58	female	2 yrs	3	1	3	2
	6	66	male	10 ms	2	1	3	1
	7	57	male	2 yrs	3	2	2	2
	8	63	female	1 yr	2	1	3	1
	9	56	male	2 yrs	2	1	3	1
	10	52	female	9 ms	3	1	3	1
A	1	59	male	9 ms	2	1	2	1
	2	29	female	18 ms	2	1	3	2
	3	35	male	10 ms	3	1	3	1
	4	72	male	1 yr	2	1	3	1
	5	67	female	11 ms	2	1	3	1
	6	59	male	1 yr	3	2	2	1
	7	65	female	14 ms	2	1	2	1
	8	62	male	11 ms	1	0	1	0
	9	37	female	1 yr	3	1	3	1
	10	69	female	18 ms	3	2	2	2

Group	No	BTX units	rTMS	Muscles injected
B	1	350	10	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis
	2	350	10	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis
	3	350	10	FCU,FCR,FDS,FDP,FPL,biceps,brachialis
	4	400	10	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis,pronator teres
	5	350	10	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis
	6	400	10	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis,pronator teres
	7	250	10	FCR,FDS,FDP,FPL,biceps
	8	400	10	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis,pronator teres
	9	350	10	FCU,FCR,FDS,FDP,FPL,biceps,brachialis
	10	350	10	FCU,FCR,FDS,FDP,FPL,biceps,brachialis
A	1	400	no	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis,pronator teres
	2	350	no	FCU,FCR,FDS,FDP,FPL,biceps,brachialis
	3	350	no	FCU,FCR,FDS,FDP,FPL,biceps,brachialis
	4	350	no	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis
	5	350	no	FCU,FCR,FDS,FDP,FPL,biceps,brachialis
	6	400	no	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis,pronator teres
	7	350	no	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis
	8	350	no	FCU,FCR,FDS,FDP,FPL,biceps,brachialis
	9	400	no	FCU,FCR,FDS,FDP,FPL,biceps,brachioradialis,pronator teres
	10	300	no	FCR,FDS,FDP,FPL,biceps,brachialis

Group	No	Range of motion (ROM)							
		baseline		week 2		week 6		week 12	
		ELBOW extention	WRIST extention	Elbow extention	Wrist extention	Elbow extention	Wrist extention	Elbow extention	Wrist Extention
B	1	ll 7(	limited ll 1(	ll 5(	ll 20	ll 2(	ll 40	ll 2(	ll 40
	2	ll 90°	limited ll 20°	70°	ll 30	40	ll 50	35	ll 50
	3	ll 60°	limited ll 15°	40°	30	20	ll 40	20	ll 40
	4	70°	limited ll 10°	40°	20	20	ll 40	15	ll 40
	5	90°	limited ll 20°	60°	20	30	ll 50	30	ll 50
	6	80°	limited ll 20°	60°	30	30	ll 50	20	ll 50
	7	70°	limited ll 30	60°	40	40	ll 60	30	ll 60
	8	90°	limited ll 20°	70°	30	30	ll 40	20	ll 40
	9	90°	limited ll 10°	70°	15	30	ll 30	20	ll 30
	10	70°	limited ll 15°	40°	30	20	ll 50	15	ll 50
A	1	70°	limited ll 2(	50°	30	40	ll 40	35	ll 40
	2	80°	limited ll 20°	50°	30	30	ll 40	30	ll 40
	3	80°	limited ll 10°	60°	30	40	ll 40	35	ll 40
	4	90°	limited ll 1(	70°	30	40	ll 45	40	ll 45
	5	80°	limited ll 20	60°	30	20	ll 50	20	ll 50
	6	80°	limited ll 10°	60°	20	30	ll 40	30	ll 40
	7	70°	limited ll 20°	50°	30	30	ll 50	20	ll 50
	8	90°	limited ll 10°	70°	40	40	ll 45	20	ll 45
	9	90°	limited ll 10°	70°	40	50	ll 40	45	ll 40
	10	70°	limited ll 10°	50°	30	30	ll 30	30	ll 30

GROUP	No.	Modified Ashworth Scale (MAS)							
B		baseline		week 2		week 6		week 12	
		Elbow	wrist	elbow	wrist	elbow	wrist	elbow	Wrist
	1	2	3	1+	2	1	1+	1	1+
	2	3	2	2	1+	1+	1	1	1
	3	1+	2	1+	1+	1	1	1	1
	4	2	3	1+	2	1	1+	1	1+
	5	3	2	2	1+	1+	1	1+	1
	6	3	2	2	1+	1+	1	1	1
	7	2	1+	2	1	2	1	1+	0
	8	3	2	2	1+	1+	1+	1	1+
	9	3	3	2	3	1+	2	1	1+
	10	2	2	1+	1+	1	1	1	0
A	1	2	2	1+	2	1	1+	1	1
	2	3	2	2	1+	1+	1+	1+	1+
	3	3	3	2	2	1+	1+	1	1+
	4	3	2	2	2	1+	1+	1+	1+
	5	3	2	2	1+	1+	1	1+	1
	6	3	3	2	2	1+	1+	1+	1+
	7	2	2	1+	1+	1+	1	1	1
	8	3	3	2	2	1+	2	1	1+
	9	3	3	2	2	1+	1+	1	1+
	10	2	3	1+	2	1	2	1	2

Group	No	Tardieu scale							
		baseline		week 2		week 6		week 12	
		Elbow	wrist	Elbow	wrist	Elbow	Wrist	Elbow	Wrist
B	1	2	4	2	3	1	2	1	2
	2	3	3	2	2	1	1	1	1
	3	2	3	2	2	1	1	1	1
	4	2	4	2	3	1	2	1	2
	5	3	3	3	3	2	1	2	1
	6	3	3	3	2	2	1	2	1
	7	2	2	2	1	2	1	1	1
	8	3	3	3	2	2	2	1	2
	9	3	4	2	3	1	2	1	2
	10	2	3	2	2	1	1	1	1
A	1	2	3	2	3	1	2	1	2
	2	3	3	3	3	2	2	2	2
	3	3	4	3	3	2	2	2	2
	4	3	3	3	3	2	2	1	2
	5	3	3	3	2	2	1	2	1
	6	3	4	3	3	2	2	1	2
	7	2	3	2	2	2	1	1	1
	8	3	4	3	3	2	2	1	2
	9	3	4	3	3	2	2	2	2
	10	2	4	2	3	1	2	1	2